

Pioneer Transfusionists of Los Angeles

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The transfusion of blood from one person to another is an accomplishment that had been dreamed of by many physicians for centuries but has only relatively recently been achieved. The first transfusion (animal to human) was given by Jean Denys of Paris in 1666¹ and was followed by a number of transfusions, some in France, but most in England. The danger of the procedure, however, was such that only about 300 transfusions had been given by the end of the 19th century, and many of those were fatal. The mortality was caused partly by the lack of knowledge of blood groups and partly because blood transfusion was limited to those cases in extremis.²

Although a few early attempts had been made as a measure of desperation, blood transfusion in the United States really began with the arteriovenous anastomosis performed by Alexis Carrel in 1908.³ This was followed by the pioneering efforts of G.W. Crile, who wrote the first book published in America on this subject.⁴ Crile, as did a number of his colleagues, used an arteriovenous anastomosis to transfer the blood from donor to recipient. Due to the difficulty of this surgical procedure and the trauma to the donor's artery, which was lost for further use, it was used infrequently and by only a few workers. Subsequently, the multiple-syringe method of Lindeman⁵ (a modification of Seeman's earlier method)⁶ allowed blood to be taken repeatedly from a donor's vein without the radial artery being permanently damaged, and was thus better accepted. The technical aspects of the procedure were less demanding and achievable by less specialized workers.

Early in this century there were only a few physicians in this country who did blood transfusions, and they managed to create a subspecialty out of the field. Some of these persons were Crile of Cleveland, Unger of New York, Minot of Boston, Curtis of Chicago and Ochsner of New Orleans. There was of course a need for such work in every major city, and in Los Angeles, the opportunity devolved on the pioneering pathologists Walter Brem and A. Hermann Zeiler.⁷

These two physicians were about as diverse as two men could be. Brem was the prototypic polished Southern gentleman. Born in North Carolina in 1875, he received a baccalaureate degree in science from the University of North Carolina in 1896. After serving in the Spanish-American War, he attended medical school at Johns Hopkins University (Baltimore), after which he became a house officer at the University Hospital under William Osler.

Zeiler was born in 1882 in the town of Sombor, Yugoslavia. At the age of 5, his parents brought him to Leadville, Colorado. On graduating from high school, the youthful stu-

dent went directly to the College of Physicians and Surgeons in New York City, where he obtained his medical degree in 1905. He interned at Sydenham Hospital in New York City for about six months.

After their training, both physicians decided to take their first job in the Canal Zone. The reasons for this undoubtedly are as complex as the reasons for any decision made by humans. On the other hand, it is possible to surmise some of the reasons. For Brem we can see a rather continuous series of stimuli. During this time the rise in technology in medicine was such that the clinical laboratory was becoming of great interest.⁸ Reisner⁹ shows that the advent of the microscope in the mid-1800s affected the field of medicine profoundly. Microbiologists quickly accepted the microscope, and their field progressed, whereas pathologists did not initially and therefore their field took a considerably longer time to develop. For this reason, in the late 1800s, microbiology, along with parasitology, was a rapidly expanding science. This change occurred especially at Johns Hopkins, where Brem trained. William Welch, MD, one of the founders of the school and hospital, was a trained microscopist and microbiologist, so he set up a pathology section that focused on microbiology and parasitology.^{10,11} Due to his enthusiasm and training, medical centers across the United States were flooded with department chairs of pathology who had trained at Johns Hopkins,¹² all of whom were oriented toward the microscope and most toward the various disciplines of microbiology. Walter Reed took postgraduate courses at Johns Hopkins and did some research there when he was curator of the Army Medical Museum in Washington, DC.¹³

All of these factors must have stirred great interest in a young medical student. Further, Brem, having been a soldier in the Spanish-American War, must have seen the US Army Sanitary Commission in action and was thus made aware of the usefulness of laboratory medicine. Last, Osler, under whom Brem took his internship, had worked with MacCallum and others on a series of studies on malaria; from that it is possible to trace his exposure to the disciplines of microbiology and infectious disease. It was almost inevitable that Brem would enter some area of infectious disease or laboratory medicine, and the Canal Zone undoubtedly provided a strong drawing force, particularly with its many close ties with Johns Hopkins Medical Center. He accepted a position in the Canal Zone at Colon Hospital in 1905.

It is more difficult to explain why Zeiler entered the Canal Zone in 1906. His training did not particularly benefit him for any laboratory area, nor was his medical school particularly noted for laboratory medicine. In fact, the position that he

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received in Ancon Hospital was that of an assistant surgeon, and he initially spent his time doing clinical medicine. His son states that the motivation may have been that his father needed a job, and one was open in the Canal Zone. In 1907 Zeiler was reassigned to the Colon Hospital at the other end of the Canal Zone, where he and Brem became co-workers in doing clinical laboratory tests.

They coauthored three papers during their lifetimes: one on intestinal amebiasis, another on influenzal meningitis and the third on the use of fasting blood donors. The first two of these were based on their Canal Zone experience. In each case Brem was the senior author and, in addition, he wrote 14 other papers and coauthored one other with F.C. Watson. Although in many cases Zeiler contributed to the work, he disliked writing and, therefore, sometimes was not listed as an author of work to which he contributed (Meyer Zeiler, MD, oral communication, October 1984).

At the end of their Canal Zone experience, the physicians decided to go to Milwaukee to set up an office. This may have been at the urging of Mrs Brem, who was originally from Milwaukee. The American Medical Association's 1911 meeting, however, was being held in Los Angeles (the first time this meeting was held in the West), and en route to Milwaukee, Brem presented a paper at the meeting on typhoid vaccine therapy for typhoid carriers. Apparently he was entranced by Los Angeles and decided to establish a laboratory in that community. Later that year he set up an office in the Security Building at Fifth and Spring Streets where, before the year was finished, he was joined by Zeiler as a partner in the practice of clinical laboratory medicine. As time went on, they provided laboratory service for many of the hospitals in the downtown Los Angeles area.

Early in their practice, they began to do blood transfusions. Their first transfusion was given on April 2, 1912,⁷ to a woman receiving care at Good Samaritan Hospital for pernicious anemia. In the account book in which they kept records of their office practice, there is recorded on December 18, 1912, the outpatient transfusion of 250 ml of blood of Moss type III to a patient, Mr S, from a donor, Miss F. By 1916, Brem was able to report that they had performed more than 200 transfusions using defibrinated blood, direct transfusion and citrated blood.¹⁴ No record exists of all the individual patients or the diseases for which they were transfused, but, in general, due to the laborious nature of the procedure, only those patients with chronic anemias such as pernicious anemia or leukemia were transfused. Yet Dr M. Zeiler comments that he knows of at least one occasion when his father did go to French Hospital to transfuse several patients who had influenza during the 1918 epidemic in an effort to "pick up their resistance." A few times, trauma cases of various types were transfused, but we have no record as to the outcome of the patients. Blood transfusions were given whenever needed. Dr Zeiler tells how his father was called out of various social gatherings or from bed at night to give transfusions.

The donors used for these transfusions were usually paid. Brem's article states that they preferred truck drivers, who were usually large men with "enormous veins." These donors were ABO grouped before being added to the donor panel, and a Wassermann test was done. The donors were then called when needed. The transfusions were done usually in the office, although some were done in various local hospitals.

The method used was a variant of the Lindeman multiple-

syringe technique.⁵ The patient and donor were placed next to each other, a needle was placed in the antecubital vein of each and a syringe full of blood was removed from the donor. The filled syringe was then passed to the other physician, who injected the blood into a needle inserted into the vein of the patient. Blood was kept from flowing from the open needle by placing the gloved finger over the end of the needle. Dr Zeiler remembers that at the start of an operation, about 25 syringes, 20-ml size, were made available. If blood began to clot, the offending syringe was rinsed in saline until it moved freely once again. Both the donor and the recipient were sterilely draped, partly in an effort to preserve sterility and partly to preserve the anonymity of the donor and of the recipient. On at least one occasion this anonymity broke down. Dr Zeiler recalls one of his father's stories of transfusing a famous opera soprano, and at the completion of the procedure, the singer approached the donor and said in her thick German accent, "Do you know that you have just given blood for the great Madame Schumann-Heink?"

It is interesting to note that, even though sodium citrate had been found to be useful as an anticoagulant of blood, Brem and Zeiler and many others still transfused blood directly without an anticoagulant. This choice has been recently discussed by Wain.¹⁵ Most of the transfusionists of that day believed (corroborated supposedly by statistics) that the use of citrate was almost always accompanied by a rather severe febrile reaction that was ascribed to the citrate. It was another ten years before the work of Seibert¹⁶ showed that it was not the citrate itself that usually caused the reaction, but rather the bacterial pyrogens that remained after cleansing the reused flasks and tubing. The introduction of disposable plastic equipment largely eliminated this hazard. It is of little wonder that, if most patients experienced febrile reactions of 3°F to 5°F and these were ascribed to the citrate, there was little interest in using the incriminated anticoagulant. Another hazard with citrate that was addressed in Brem's article was the use of the 1% formula advocated by Weil.¹⁷ It was eventually found that this concentration could be toxic and that Lewishohn's formula¹⁸ was much better tolerated.

The unique aspect of the Brem-Zeiler transfusion procedure was their early reliance on laboratory testing. It is difficult today to perceive just how crude the methods were during those early years. Landsteiner,¹⁹ writing in 1901, had shown the existence of three naturally occurring blood groups in humans. Work by De Castello and Sturli²⁰ in 1902 added the fourth group to what we now know as the ABO system. Yet Crile⁴ in his 1909 book described using a simple hemolysin test in some cases and does not even mention the existence of blood groups. Hektoen in 1907 urged that blood of compatible groups should be transfused, but did not elaborate beyond that.²¹ In 1908 Ottenberg listed compatibility testing as an addition to his report about a method of doing arteriovenous anastomoses, but it was not used at Mount Sinai Hospital. He writes,

As I was in the laboratory, I offered to do the compatibility tests, but many of the surgeons did not accept the offer. They felt that since Crile had done a large series of transfusions without tests (and with only a few cases of hemolysis and no deaths) they ought to be free from interferences by the laboratory men. It took about five years of campaigning, experimenting and a few accidents to convince the medical public that blood tests before transfusion were essential.^{22(p266)}

Another obstacle to crossmatching was the personal nature of blood transfusions. As has been stated previously, only a

few persons in each city performed transfusions. Most of these physicians were highly paid and very probably did not wish to share the income with others. Further, there was inadequate experience to show that safety would be increased by a nonsurgical technique. In this light, the comments of Ottenberg become particularly relevant. Crossmatching as we know it today did not gain much nationwide popularity until just before World War II.

Meanwhile, Brem and Zeiler in 1911 developed their method of blood group testing.¹⁴ This became well enough known that it is mentioned by Ottenberg, who says, "following the suggestion of Brem of San Francisco [*sic*] it was thought sufficient to determine the group of patient and donor."²² (p 267) Yet, rather than a simple determination of the blood group, the method was unique and was aided somewhat by the fact that Brem had group B blood and that Zeiler had group A. Thus, they always had a set of known reagents available for typing. Basically, the blood of the patient was crossmatched with the blood of either Brem or Zeiler. By simply observing the agglutination of the erythrocytes and the serum of both persons, the blood type of the patient could be determined. Blood from a donor of the identical type was always used. Why were these physicians doing crossmatches when the medically advanced Easterners were not? Undoubtedly the major reason was that there were no other transfusionists who had vested interests in preserving the status quo and who would thus interfere.

All early records kept in the Brem-Zeiler laboratory used the Moss nomenclature for the four major blood groups. This system, described in 1910,²³ became very popular in the western United States and used Roman numerals rather than letters to indicate the blood groups. It was probably adopted by Brem and Zeiler because of Moss's association with Johns Hopkins University and because Brem was well acquainted with Moss and his work.

In their subsequent paper dated 1928,²⁴ Brem, Zeiler and their new associate, Hammack, discuss the occurrence of transfusion reactions and list some cases that they had observed in a series of more than 4,000 transfusions. It is interesting that many of these reactions are the same types seen today. They report, however, that 20% of their patients had a fever of more than 1°F after transfusion, which is a much higher percentage. The main purpose of their article was to show that many of the reactions they encountered could be eliminated by using fasting donors. At the end of the paper, they quote Dorn, who believed that "incompatible leukocytes" caused febrile reactions. Brem and Zeiler postulate that "digestive leukocytosis" might increase the number of leukocytes present and might give a more severe reaction. This work was not confirmed, and no one has been able to show a decrease of reactions with fasting donors. Rather, it is the unpublished experience of many that donors who have not

eaten have a higher incidence of reactions, and therefore almost all blood banks today encourage a donor to eat before donating.

The time for this extremely labor-intensive and awkward procedure was drawing to a close. In 1937 Fantus established the first blood bank for the actual storing of anticoagulated blood for indirect transfusion in Cook County Hospital, Chicago.²⁵ World War II showed the great need for human blood and blood products in resuscitating trauma patients and stimulated the establishment throughout the world of blood banks as we know them. During that time period, direct transfusions came to an end. Today in the United States more than 10 million units of blood and blood products are transfused annually. Yet none of this might ever have happened if it had not been for this small band of physicians who spent much of their lives studying methods of doing safer and better blood transfusions.

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